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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant: Christine Van Broeckhoven et al.
Serial No: Serial No. 09/581,500
Confirmation No.: 9967
Filed: November 14, 2000
For: MOOD DISORDER GENE
Examiner: Carla J. Myers
Art Unit: 1634

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

**DECLARATION OF CHRISTINE VAN BROECKHOVEN
UNDER 37 C.F.R. §1.132**

I, Christine Van Broeckhoven, declare that:

- 1. I am a co-inventor of the above-identified patent application (USSN 09/581,500, referred to herein as "the patent application").**
- 2. I am currently the Scientific Director of the Department of Molecular Genetics at the University of Antwerp, Belgium. I have conducted research in the field of molecular genetics for over 20 years and have co-authored more than 400 peer-reviewed papers in the field. I also act as a Scientific Advisor to a number of different organizations, including the Research Advisory Board of the European Union. In the past I have served as a Vice President and Board member of the International Society of Psychiatric Genetics. Further details of my extensive experience in the field are set out in the attached Curriculum Vitae.**

3. Claim 1 currently on file in the patent application is concerned with a method for identifying human coding regions/genes associated with bipolar disorder which involves identifying the position of a coding region/gene in a specific portion of human chromosome 18, which can be compared to an "equivalent region of DNA" from a person afflicted with a bipolar disorder. Based on my experience and knowledge as one skilled in the art of human molecular genetics, and more specifically genetic linkage analysis, I would understand the term "equivalent region" as used in this context as referring to the region of DNA which occupies the same physical location, i.e. the same genetic locus, in the genome of the afflicted individual.
4. The human genome has been extensively mapped, both genetically and physically, such that the genetic and/or physical map positions of a given coding region can be readily described, for example by reference to chromosomal markers. Given that the physical and genetic map order of genes in the genome of two individuals of the same species is usually conserved (except in the case of rare chromosome translocation events) it is routine for one of skill in the art to identify genes occupying the same physical location or genetic locus in two different individuals of the same species such that comparisons can be made between the equivalent genes in two different individuals.
5. In fact, it is generally not necessary to know the precise physical or genetic map location of a given gene in order to make comparisons between equivalent regions of DNA in equivalent genes from two individuals of the same species. Once a particular gene/coding region has been characterized at the level of nucleotide sequence, such that a species consensus sequence is available for the gene (or a fragment of it or even just the encoded cDNA), then it is straightforward to make sequence comparisons between the equivalent regions of DNA from two or more individuals of the same species without the need for actual physical or genetic

mapping of the gene within the genome of each individual. By way of example, it is straightforward simply to sequence equivalent regions of DNA representing the whole or a sub-fragment of a gene/coding region in two or more individuals of the same species and to compare the sequences thus obtained. If a particular genetic polymorphism (e.g. a SNP) is known to occur within the coding region of interest then it is even more straightforward to make comparisons between equivalent regions of DNA individuals of the same species simply by genotyping the individuals for this polymorphism.

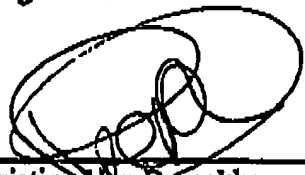
6. The process of making comparisons between equivalent regions of DNA in individuals who manifest disease symptoms and control individuals is key to the identification of susceptibility genes for complex diseases. Thus, it is my considered opinion from my extensive experience in this field that the meaning of the term "equivalent region of DNA" in the context in which it is used in the claims of the patent application has a clear meaning to one skilled in the art.
7. The experimental section of the present application describes a linkage study in a Belgian family denoted MAD31 which was carried out by myself and the co-inventors of the patent application in order to narrow down the region of linkage for bipolar disorder and related mood disorders on human chromosome 18. This study was based on a linkage analysis in which a number of STR polymorphic markers were genotyped in members of family MAD31 and two-point lod scores were calculated under three different modes of inheritance. The lod score analysis gave positive results with all markers. The highest lod score of +2.01 at $\theta=0.0$ was obtained with markers D18S1113, D18S876 and D18S477 under inheritance model 1, which is described in the present application at page 26, lines 5-14. θ is a value describing the genetic distance between the disease and a marker. $\theta=0.0$ corresponds to a marker that is very close to the disease locus, i.e. no recombination occurs between the two markers.

8. I submit from my knowledge as one skilled in the art of human genetics and genetic linkage analysis that the lod score of +2.0 was indicative of significant linkage in this study, taking into account the design of the particular linkage study carried out in family MAD31.
9. The linkage study described in the experimental section of the present application did not involve a whole genome scan. Rather, the linkage study focused on a particular region of human chromosome 18, with a view to narrowing down the region of linkage to bipolar disorder and related mood disorders. The maximum lod score of +2.01 at $\theta=0.0$ was considered indicative of significant linkage in the context of this study in the family MAD 31.
10. I am aware of the publication by Lander and Kruglyak (Nature Genetics, Volume 11, November 2005). The authors of this paper proposed a set of standard thresholds for declaring "significant" or "suggestive" linkage when mapping loci underlying complex genetic traits. In the context of a genome-wide scan, Lander and Kruglyak propose a threshold lod score of 3.6 for declaring significant linkage. However, it is stated at page 245, left-hand column that in the case of a replication study carried out over a region of a single chromosome the threshold for significant linkage will be different. For an interval of 20 cM a P value of $P=0.01$ is suggested for declaring confirmation of linkage at the 5% level.
11. Lod scores represent one way of expressing the results of a linkage study statistically. Lod scores reflect the *ratio* of two different probabilities. A lod score of 3.0 means that the observed data is 10^3 -fold more likely to arise under a specified hypothesis of linkage than under the null hypothesis if no linkage. The results of linkage studies can also be expressed statistically in terms of a P value, which is the absolute probability of encountering as large a lod score (as is

observed in the linkage study) under the null hypothesis of no linkage. Generally there is no need to state both the lod score and the P value for a given linkage study.

12. In the MAD 31 linkage study a lod score of 2.0 corresponds to a P value of 0.01 which according to the criteria of Lander and Kruglyak is sufficient for declaring confirmation of linkage at the 5% level.
13. Lander and Kruglyak also state on page 245 that replication studies should always state their power to detect the proposed effect with the given sample size. The term "power" in this context is referring to the power of association samples not of family based linkage studies *per se*. I do not consider this statement to be of any relevance to the family study disclosed in the present application and do not agree with the Examiner's assertion that it is not possible to properly evaluate the significance of the disclosed LOD scores.
14. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

13/10/2005
Date


Christine Van Broeckhoven

CURRICULUM VITAE

NAME Christine Van Broeckhoven

DATE OF BIRTH April 9th, 1953

CITIZENSHIP Belgian

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CURRENT AFFILIATIONS University of Antwerp (UA)
 Institute Born-Bunge (IBB)
 Flanders Interuniversity Institute for Biotechnology (VIB)

EDUCATION

Degree	Institution	Year Awarded
Bachelor in Chemistry	University of Antwerp (RUCA)	1973
Master in Biochemistry	University of Antwerp (UIA)	1975
Ph.D. Molecular Biology	University of Antwerp (UIA)	1980
D.Sc. Molecular Genetics	University of Antwerp (UIA)	1994

SCIENTIFIC CARREER

Position	Institution	Year
Ph.D. Student	UIA	1975-1979
Postdoctoral Fellow	Provincial Institute of Hygiene	1979-1982
Research Assistant	UIA	1983-1989
Research Fellow	National Fund of Scientific Research (NFWO)	1989-1995
Assistant Professor	UIA	1990-1994
Research Director	Institute Born-Bunge (IBB)	1990
Associate Professor	UIA	1995-1996
Scientific Director	Dept. of Molecular Genetics (VIB8) Flanders Interuniversity Institute for Biotechnology (VIB)	1995
Professor	UIA	1997-1998
Ordinary Professor	UIA	1999

PROFESSIONAL CARREER

Position	Company	Period
Consultant	Innogenetics Inc.	1990-1993
Consultant	Janssen Pharmaceutics	1995-2001

SCIENTIFIC PUBLICATIONS (*per 01.06.2005*)

Articles in Books > 46
 Articles in International Journals > 413
 Articles in National Journals > 29

PhD: 38**PRIZES**

- **Prize Divry** of the Belgian Society of Neurology, Brussels, Belgium, October 21, 1991: 'Gene technology and Alzheimer disease'.

- Co-recipient of the **Potamkin Prize** of the American Academy of Neurology, New York, USA, April 27, 1993: 'APP mutations and cerebral haemorrhages'.
- **Scientific Prize Joseph Maisin** of the National Fund of Scientific Research (NFSR), Brussels, Belgium, July 5, 1995: Medical and Biological Sciences 'Molecular Genetics of Alzheimer disease: Identification of genes and gene mutations'.
- **Prize Marie-Thérèse De Lava**, of the King Boudewijn Foundation, Brussels, Belgium, November 21, 1995: Ageing 'Molecular Genetics of Alzheimer Disease'.
- Co-recipient of the **Scientific Prize Upjohn Inc.** of the National Fund for Scientific Research (NFSR), Brussels, Belgium, December 18, 1995 'Molecular genetic research of neurodegenerative disorders: peripheral neuropathy of Charcot-Marie-Tooth disease (CMT type 1)'.
- Co-recipient of the **Lundbeck-Prize** of the Belgian College of Neuropsychopharmacology and Biological Psychiatry (BCNBP), Brussels, Belgium, June 3, 1997: The presenilin genes: A new family involved in Alzheimer disease pathology'.
- **Special Honor Award for Women in Science 2002**, with the support of L'Oréal/Unesco, Brussels, Belgium, January 23, 2003
- **55th Ark Prize for Freedom of Speech 2005**, May 4, 2005

HONORS

- **Alzheimer Professor Chair**, University of Leiden, Department of Neurology 1996
- **Associate Member** of the Royal Flemish Academy of Sciences and Art- Belgium, 1999
- **Guest Scientist** at The Scripps Research Institute La Jolla, San Diego, USA, 2001

PROFESSIONAL SOCIETY ACTIVITIES

International

Current Activities

European Charcot-Marie-Tooth Consortium: Consortium Leader and President of the Steering Committee, 1991
Federation of the European Neurological Societies (FENS): Scientific Panel on 'Genetics, including Molecular Genetics', 1993

European College of Neuropsychopharmacology (ECNP), 20th ECNP Congress, Scientific Programme Committee, 2005-2007

EU – Expert Group on Women in Science, Life Sciences, 2002

EU – Evaluator – VI frame work, 2002-2006

EU – Evaluation Panel – EU program on 'Life Sciences: Genomics and Biotechnology for Health' – Area 'Fundamental Genomics', 2004

EU – European Research Advisory Board (EURAB), 2004 - 2007

Alzheimer Europe Expert Advisory Panel, 2003

The International Society of Psychiatric Genetics: Board, 1994

The International Society of Psychiatric Genetics: International Scientific Programme Committee, 1996, 1998-1999, 2001-2005

The International Society of Psychiatric Genetics: Vice President, 2000

USA, Faculty of 1000 Medicine: Faculty member and member of the Evaluation Board, Section Head 'Alzheimer's disease', 2004

USA, Alzheimer Research Forum, Member of the Scientific Advisory Board, 2004

Past Activities

European Society of Human Genetics: Board, 1992-1997

European Society of Human Genetics: Chairperson of the Scientific Programming Committee, 1993-1994

European Society of Human Genetics: Scientific Programming Committee, 1993-1997

European Neuro-Muscular Centre (ENMC): Research Committee, 1994-1999

EU – Concerted Action on 'Cellular Aging and Disease' (EURAGE): Biology of Aging Group, 1989-1991

EU – BIOMED2 Ad Hoc Working Group on Human Genome Research, 1995-1996

EU – Evaluation panel – EU Projects Human Genome Analysis, 1996

EU – Evaluator – IV frame work – BIOMED2 programme, 2nd Call, 1996-1998

EU – Evaluation Panel – EU Training and Mobility of Researchers – Life Sciences, 1997
 EU – National Contact Person of BIOMED2 on ‘Ageing’ for the Ad hoc Advisory Committee (AHAC) to CREST for the co-ordination of RTD Policies, 1998
 EU – Evaluator – V frame work, 1999-2000
 EU – High Level Expert Group I on Chronic and degenerative diseases, genomics, neurosciences, 1999-2003
 EU – Expert for the Assessment of Expressions of Interest (EoI’s) ‘Studying the brain and combating diseases of the nervous system’, 2002
 Alzheimer Europe – Response to NICE recommendations, Member of the Alzheimer Europe Expert Advisory Panel, 2005
 Human Frontier Science Program (HFSP), EU delegate to the Council of Scientists 2001-2004
 Human Genome Organisation (HUGO): Community Editor of chromosome 21, 1993-1998
 The International Society of Psychiatric Genetics: International Advisory Committee, 1993
 The International Society of Psychiatric Genetics: Chair & Local Organiser Xth World Congress on Psychiatric Genetics, 2002
 Alzheimer’s Disease and Related Disorders: International Advisory Committee, 1994
 Alzheimer’s Disease and Related Disorders: Scientific Programme Committee, 1997-1998
 USA - Charcot-Marie-Tooth Association (CMTA): Medical Board, 1998-2004

National

Current Activities

Institute Born-Bunge (IBB): Scientific Advisory Board, 1990
 Flanders Interuniversity Institute for Biotechnology (VIB): Board of Scientific Directors, 1995
 Flemish Institute for the advancement of Scientific and Technological Research in Industry (IWT): Evaluator of the PhD & Postdoc fellowships, 1995
 Fund for Scientific Research – Flanders (FWO): Commission Medical Cell Biology and Genetics 1997 – 2006
 National Fund for Scientific Research (NFSR): Working party ‘Ethical genetics’, 1994
 Federal Ministry of Science Policy, Member of the High Level Group 3% for Research, 2004
 Alzheimer Liga Belgium: Scientific Advisory Board, 1990
 CMT-Belgium: Scientific Advisory Board, 1991
 Medical Women’s Association of Belgium: Board, 1995
 Belgian College of Neuropsychopharmacology and Biological Psychiatry: Councillor, 2000
 King Boudewijn Foundation – Workgroup Human Genome, 2001
 Belgian division – EU-project ‘Meeting of Minds’, Advisory Committee, 2005
 International Alzheimer Research Foundation (IARF): Member of the Scientific Advisory Board, 1996
 International Alzheimer Research Foundation (IARF): Chair Scientific Advisory Board (SAB), 2003
 Germany - German Ministry for Science – Kompetenznetzwerk ‘Mednet Stroke’: Advisory Board, 1999
 Germany - Max-Delbrück-Center for Molecular Medicine, Berlin: Member of the Expert group, 2001
 Germany, Tübingen, Meeting: Alzheimer: 100 years and beyond, Member of the Scientific Advisory Board, 2005-2006
 Sweden - Center for Molecular Medicine, Karolinska Institute: Advisory Board, 1996
 The Netherlands: Netherlands Organisation for Scientific Research (NWO) – Human Genome Analysis’: Evaluation Committee, 1997
 The Netherlands: Netherlands Organisation for Scientific Research (NWO) – The Research Institute ‘Diseases of the elderly’: International Expert Committee, 1999
 The Netherlands, Royal Dutch Academy of Sciences (KNAW) – Multifactorial disorders in the genomic-era’, member of the commission of investigations, 2003
 UK – Alzheimer Research Charity: Charity Trustee, 1998
 USA, Mayo Clinic Jacksonville, Program Project ‘Genetic and functional studies to determine the role of tau in PSP’, Member of the External Advisory Board, 2004

Past Activities

Provincial Centre for the Detection of Metabolic diseases: Steering Group, 1990-1993
 Institute for Scientific Research in Industry and Agriculture (IWONL), Evaluator of fellowships, 1991-1993
 Institute for hygiene and epidemiology: ad hoc expert group ‘Recombination viral vectors, virosomes, recombinant vaccines, gene therapy’ of the provisional bio-safety council, member, 1996-2000
 Flemish Board of Scientific Policy (VRWB): Member, 2000-2002
 Belgian Society for Neurology: Jury Member Divry, 1994

Belgian Society of Biochemistry and Molecular Biology: Board Member, 1996-1999
Administration for Science and Innovation (AWI), Jury Member of the Commission, 1999-2001
Department of the Federal Government - Public Health, Safety of the food chain en environment, project:
‘Development of a more performance genotyping essay of scrapie sensitivity, member of the expert group
2003
The Royal Academy of Medicine – Belgium, Jury Member for the Prize of the Flemish Scientific Foundation for
Biomedical Sciences 2004
MILQTL-programme: Review Panel, 1994 – 1998
Germany - 11.Jahrestagung der Deutschen Gesellschaft für Humangenetik: Scientific Programme Committee,
1998 – 1999
Germany - National Medical Network on Dementias by the German Federal Ministry of Education and Research
(BMBF): International Advisory Board, 2000
Finland – Academy of Finland, Research Council for Health: Scientific Expert, 2002
Finland, University of Tampere, member of the Research Evaluation panel, ‘Medical School & Institute of
Medical Technology’, 2004
France, Association Française contre les Myopathies (AFM): Group ‘Maladies du motoneurone et neuropathies
héréditaires sensitive-motrice’: Member, 1998-2002
Italy, Italian Téléthon Foundation: Scientific Committee, 2001-2002
Sweden, University of Umeå, Faculty of Medicine and Odontology – Applications for Professorship in Medical
Genetics: Outside Expert/Evaluator, 2000-2001
The Netherlands - Internationale Stichting Alzheimer Onderzoek (ISAO): Scientific Advisory Board, 1995-1997
The Netherlands – Ministry of Public Health: Gezondheidsraad: Commission DNA-Diagnostics, 1995 – 1998
UK – Alzheimer’s Research Trust: Scientific Advisory Board, 1993-1997

PROFESSIONAL MEMBERSHIPS

International

European Neuroscience Association, 1991
European Society of Human Genetics, 1991
Federation of European Neuroscience Societies, 1996
American Society of Human Genetics, 1987
American Association for the Advancement of Science, 1991
Society for Neuroscience, 1990
The International Society of Psychiatric Genetics, 1992
World Federation of Societies of Biological Psychiatry, 2005

National

Belgian Society of Biochemistry, 1988
Belgian Society of Neurology, 1990
Belgian Society for Cell Biology, 1994
Belgian Society for Neuroscience, 1996
Belgian College of Neuropsychopharmacology and Biological Psychiatry, 2000
Belgian Society for Human Genetics, 2002
Stichting Lieve Nijs vzw: Leven met dementia, 1993
The Society for Forensic Haemogenetics, 1988-1989

GRANTS

Supervisor

Special Research Fund – UA/UIA
Emerging Technology Centre (VLAB)
Flanders Interuniversity Institute for Biotechnology (VIB)
Fund for Medical Scientific Research (FGWO)
Fund for Scientific Research – Flanders (FWO)
National Fund for Scientific Research (NFWO)
Lotto Krediet
Ministry of the Flemish Community- Education- Concerted Action (GOA)
Ministry for Programming Scientific Policy (DPWB)

The Federal Office for Scientific, Technical and Cultural Affairs (DWTC)
 Medical Foundation Queen Elisabeth (GSKE)
 International Alzheimer Research Foundation (IARF)
 Innogenetics
 Janssen Research Foundation (JRF)
 Association Française contre les Myopathies (AFM)
 European Science Foundation (ESF)
 Commission of the European Communities (EEC)
 American Health Assistance Foundation (AHAF)
 Muscular Dystrophy Association, USA (MDA)
 Focused Giving Programme, Johnson & Johnson
 Alzheimer Association (AA)

Co-supervisor

Fund for Collective Scientific Research (FKFO)
 Netherlands Organization for Scientific Research (NWO)
 Hersenstichting Nederland
 Internationale Stichting Alzheimer Onderzoek (ISAO)
 Alzheimer Association (AA)

PATENTS

European

- European Patent Application EP 91/401220.8 Patent: 'Process for the in vitro diagnosis of chromosomal anomalies liable to be correlated with CMT1a disease', Date of Filing: 7.5.1991, Applicant: Innogenetics, Inventors: **Van Broeckhoven, C.**, Raeymaekers, P., De Jonghe, P., Martin, J-J.
- European Patent Application EP 92/400771.9 Patent: 'Mutated form of the beta-amyloid precursor protein gene', Date of Filing: 20.3.1992, Applicant: Innogenetics, Inventors: **Van Broeckhoven, C.**, Martin, J-J., Hendriks, L., Cras, P.
- European Patent Application EP 97/268.04.9, Patent: 'Mood disorder gene', Date of Filing: 18.12.1997, Applicant: Flanders Interuniversity Institute for Biotechnology (VIB), Inventors: Del-Favero, J., Raeymaekers P., Van Broeckhoven, C.
- European Patent Application EP 00/202362.0, Patent: 'A novel APP mutation associated with an unusual Alzheimer's disease pathology', Date of Filing: 06.07.2000, Applicant: Flanders Interuniversity Institute for Biotechnology (VIB), Inventors: Kumar-Singh, S., De Jonghe, C., Cruts, M., Van Broeckhoven, C.
- European Patent Application EP 01/203558.0, Patent: 'Novel brain expressed CAP-2 gene and protein associated with bipolar disorder', Date of Filing: 17.09.2001, Applicant: Janssen Pharmaceutics, Inventors: Del-Favero, J. & Van Broeckhoven, C.
- European Patent Application EP 01/202214.1, Patent: 'Novel brain expressed NCAG1 gene and protein associated with bipolar disorder', Date of Filing: 11.06.2001, Applicant: Janssen Pharmaceutics, Inventors: Del-Favero, J. & Van Broeckhoven, C.
- European Patent Application EP 02/077724.9, Patent: 'Diagnostic test for the detection of peripheral Neuropathy', Date of Filing 09.07.2002, Applicant: Flanders Interuniversity Institute for Biotechnology (VIB), Inventors: C. Van Broeckhoven, V. Timmerman & P. De Jonghe
- European Patent Application EP 03076033.4 (second priority), Patent: 'Diagnostic test for the detection of peripheral Neuropathy', Date of Filing 08.04.2003, Applicant: Flanders Interuniversity Institute for Biotechnology (VIB), Inventors: C. Van Broeckhoven, V. Timmerman & P. De Jonghe
- European Patent Application EP 03104181.7, Patent: 'Diagnostic tests for the detection of motor neuropathy', Date of Filing 13.11.03, Applicant: Interuniversity Institute for Biotechnology (VIB), Inventors: Van Broeckhoven, C., Timmerman, V., De Jonghe, P. & Irobi, J.
- European Patent Application EP 04102066.0, Patent: 'Diagnostics based on a dementia-causing gene', Date of Filing 12.05.2004, Applicant: Flanders Interuniversity Institute for Biotechnology (VIB), Inventors: R. Rademakers, M. Cruts & C. Van Broeckhoven

- European Patent Application EP 04102088.4, Patent: 'Diagnostics based on an epilepsy causing gene', Date of Filing 13.05.2004, Applicant: Flanders Interuniversity Institute for Biotechnology (VIB), Inventors: L. Claes, P. De Jonghe & C. Van Broeckhoven

International

- US Patent Application 08/133.248, Patent: 'Mutated form of the beta-amyloid precursor protein gene', Date of Filing: 08.10.1993, Applicant: Innogenetics, Inventors: Van Broeckhoven, C., Martin, J-J., Hendriks, L., Cras, P.
- International Patent Application PCT/EP 98/08543, Patent: 'Mood disorder gene', Date of Filing: 17.12.1998, Applicant: Flanders Interuniversity Institute for Biotechnology (VIB), Inventors: DelFavero, J., Raeymaekers, P., Van Broeckhoven, C.
- International Patent Application PCT/EP 99/04106, Patent: 'Novel fragmentation vectors and uses thereof', Date of Filing: 11.06.1999, Applicant: Flanders Interuniversity Institute for Biotechnology (VIB), Inventors: Del-Favero, J., Van Broeckhoven, C.
- International Patent Application PCT/EP01/07830, Patent: 'A novel APP mutation associated with an unusual Alzheimer's disease pathology', Date of Filing 06.07.2001, Applicant: Interuniversity Institute for Biotechnology (VIB), Inventors: Kumar-Singh, S., De Jonghe, C., Cruts, M., Van Broeckhoven, C.
- International Patent Application JAB1746-PCT, Patent: 'Novel brain expressed gene and protein associated with bipolar disorder', Date of Filing 17.09.02, Applicant: Janssen Pharmaceutics, Inventors: DelFavero, J. & Van Broeckhoven, C.
- International Patent Application PCT/EP03/50290, Patent: 'Diagnostic test for the detection of peripheral Neuropathy', Date of Filing 08.07.03, Applicant: Interuniversity Institute for Biotechnology (VIB), Inventors: Van Broeckhoven, C., De Jonghe, P., Timmerman, V. & Verhoeven, K.
- US & CA Patent Application PCT/EP02/10667, Patent: 'Brain expressed CAP-2 gene and protein associated with bipolar Disorder', Date of Filing 15.01.04, Applicant: Janssen Pharmaceutica, Inventors: Del-Favero, J. & Van Broeckhoven, C.
- Published Patent WO 2004/005541, Patent: 'Diagnostic test for the detection of peripheral Neuropathy', Date of Filing 15.01.04, Applicant: Interuniversity Institute for Biotechnology (VIB), Inventors: Van Broeckhoven, C., De Jonghe, P., Timmerman, V. & Verhoeven, K.

GRANT REVIEWER

National Health and Medical Research Council, Australia
 Fonds zur Förderung der Wissenschaftlichen Forschung, Austria
 Alzheimer Association, Canada
 Colciencias, Colombia
 Association Française contre les Myopathies, France
 Alzheimer Forschung Initiative (AFI), Germany
 The Health Research Board, Ireland
 The Israel Science Foundation, Israel
 The Italian Ministry for University and Scientific Research, Italy
 The National Research Council, Portugal
 Swiss National Science Foundation, Switzerland
 Internationale Stichting Alzheimer Onderzoek (ISAO), The Netherlands
 Netherlands organization for Scientific Research (NWO), The Netherlands
 Action Research, UK
 Medical Research Council (MRC), UK
 The Muscular Dystrophy Group, UK
 The Wellcome Trust, UK
 Alzheimer Association, USA
 Human Frontier Science Program

EDITORIAL BOARDS**International**

Alzheimer's and Dementia: Journal of the Alzheimer' Association, Member of the Editorial Advisory Board, 2005

American Journal of Alzheimer's disease: Member of the Research Editorial Board, 1997

European Journal of Human Genetics: Member of the Editorial Board, 1996

Genes, Brain and Behavior: Member of the Editorial Board, 2001

Human Genetics: Member of the Editorial Board, 1998

Human Molecular Genetics: Member of the Editorial Board, 2000 - 2004

Human Mutation: Communicating Editor, 1998

Neurobiology of Disease: Member of the Editorial Board, 1993

Neurodegenerative Diseases: Member of the Editorial Board, 2004

Neurogenetics: Member of the Editorial Board, 2004

NeuroMolecular Medicine: Co-Editor, 2001

Psychiatric Genetics: Member of the Editorial Board, 2002

National

Acta Neurologica Belgica: Member of the Advisory Board, 1993

Mediator plus ultra, Scientific Advisory Board, 2003

Neuropraxis – Neurowetenschappen in de praktijk, Member of the Scientific Advisory Board, 1996

SELECTED KEY REFERENCES (IF > 10)

- Venken,T., Del-Favero,J., Claes,S., Sluijs,S., Paterson,A., van Duijn,C., Adolfsson,R., **Van Broeckhoven,C.**: Genome wide scan for affective disorder susceptibility loci in families of a northern Swedish isolated population. *American Journal of Human Genetics* 76: 237-248 (2005) (I.F.: 11.602)
- Irobi,J., Van Impe,K., Seeman,P., Jordanova,A., Dierick,I., Verpoorten,N., Michalik,A., De Vriendt,E., Jacobs,A., Van Gerwen,V., Vennekens,K., Mazanec,R., Tournev,I., Hilton-Jones,D., Talbot,K., Kremensky,I., **Van Broeckhoven,C.**, Gettemans,J., De Jonghe,P., Timmerman,V.: Hot spot residue in small Heat Shock Protein 22 causes lower motor neuron disease. *Nature Genetics* 36(6): 597-601 (2004) (I.F.: 26.494)
- Lambrechts,D., Storkebaum,E., Morimoto,M., Del-Favero,J., Desmet,F., Thijs,V., Wyns,S., Marklund,S.L., Andersson,J., van Marion,I., Al-Chalabi,A., Bornes,S., Musson,R., Hansen,V., Beckman,L., Adolfsson,R., Singh Pall,H., Prats,H., Rutgeerts,P., Awata,T., Scambler,P., Leigh,N., Lang-Lazdunski,L., Shaw,C., Moons,L., Vlietinck,R., Morrison,K.E., Robberecht,W., **Van Broeckhoven,C.**, Collen,D., Andersen,P.M., Carmeliet,P.: VEGF is a modifier of amyotrophic lateral sclerosis in mice and humans, and protects motor neurons against ischemic death. *Nature Genetics* 34(4): 383-394 (2003) (I.F.: 26.711)
- Segurado,R., Detera-Wadleigh,S.D., Levinson,D.F., Lewis,C.M., Gill,M., Nurnberger,Jr, Craddock,N., DePaulo,J.R., Baron,M., Gershon,E.S., Ekholm,J., Cichon,S., Turecki,S., Claes,S., Kelsoe,J.R., Schofield,P.R., Badenhop,R.F., Morissette,J., Coon,H., Blackwood,D., Curtis,D., McInnes,L.A., Foroud,T., Edenberg,H., Reich,T., Rice,J., Goate,A., McInnis,M., McMahon,F.J., Badner,J.A., Goldin,L.R., Phil Bennett,P., Willour,V., Zandi,P., Liu,J., Gilliam,C., Juo,S-H., Berrettini,W.H., Yoshikawa,T., Peltonen,L., Lönngqvist,J., Nöthen,M.M., Schumacher,J., Windemuth,C., Rietschel,M., Propping,P., Alda,M., Grof,P., Rouleau,G.A., Del-Favero,J., **Van Broeckhoven,C.**, Mendlewicz,J., Adolfsson,R., Spence,M.A., Luebbert,H., Adams,L.J., Donald,J.A., Mitchell,P.B., Barden,N., Shink,E., Byerley,W., Muir,W., Visscher,P., Macgregor,S., Gurling,H., Kalsi,G., McQuillan,A., Escamilla,M.A., Reus,V.I., Leon,P., Freimer,N.B., Ewald,H., Kruse,T.A., Mors,O., Radhakrishna,U., Blouin,J.-L., Antonarakis,S.E., Akarsu,N.: Genome Scan Meta-Analysis of Schizophrenia and Bipolar Disorder, Part III: Bipolar Disorder. *American Journal of Human Genetics* 73(1): 49-62 (2003) (I.F.: 10.649)
- Dermaut,B., Theuns,J., Sleegers,K., Hasegawa,H., Van den Broeck,M., Vennekens,K., Corsmit,E., St. George-Hyslop,P., Cruts,M., van Duijn,C.M., **Van Broeckhoven,C.**: The gene encoding nicastrin, a major γ -secretase component, modifies risk for familial early-onset Alzheimer's disease in a Dutch population-based sample. *American Journal of Human Genetics* 70: 1568-1574 (2002) (I.F.: 10.649)
- Van Goethem,G., Dermaut,B., Löfgren,A., Martin,J.J., **Van Broeckhoven,C.**: Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA deletions. *Nature Genetics* 28: 211-212 (2001) (I.F.: 29.6)
- Claes,L., Del-Favero,J., Ceulemans,B., Lagae,L., **Van Broeckhoven,C.**, De Jonghe,P.: De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. *American Journal of Human Genetics* 68: 1327-1332 (2001) (I.F.: 10.542)
- Timmerman,V., De Jonghe,P., **Van Broeckhoven,C.**: Of giant axons and curly hair. *Nature Genetics* 26: 254-255 (2000) (I.F.: 30.91)
- Croes,E.A., Dermaut,B., van der Cammen,T.J.M., **Van Broeckhoven,C.**, van Duijn,C.M.: Genetic testing should not be advocated as a diagnostic tool in familial forms of dementia. *American Journal of Human Genetics* 67: 1033-1035 (2000) (I.F.: 10.35)
- Dermaut,B., Cruts,M., Slooter,A.J.C., Van Gestel,S., De Jonghe,C., Vanderstichele,H., Vanmechelen,E., Breteler,M.M., Hofman,A., van Duijn,C.M., **Van Broeckhoven,C.**: The Glu318Gly substitution in presenilin 1 is not causally related to Alzheimer disease. *The American Journal of Human Genetics* 64: 290-292 (1999) (I.F.: 10.426)
- Ott,A., Slooter,A.J.C., Hofman,A., van Harskamp,F., Witteman,J.C.M., **Van Broeckhoven,C.**, van Duijn,C.M., Breteler,M.M.B.: Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam study. *The Lancet* 351: 1840-1843 (1998) (I.F.: 11.793)
- Klaver,C.C.W., Kliffen,M., van Duijn,C.M., Hofman,A., Cruts,M., Grobbee,D.E., **Van Broeckhoven,C.**, de Jong,P.T.V.M.: Genetic association of apolipoprotein E with age-related macular degeneration. *American Journal of Human Genetics* 63: 200-206 (1998) (I.F.: 10.869)

- Reiter,L.T., Hastings,P.J., Nelis,E., De Jonghe,P., **Van Broeckhoven,C.**, Lupski,J.R.: Human meiotic recombination products revealed by sequencing a hotspot for homologous strand exchange in multiple HNPP deletion patients. *American Journal of Human Genetics* 62: 1023-1033 (1998) (I.F.: 10.869)
- Tysoe,C., Whittaker,J., Xuereb,J., Cairns,N.J., Cruts,M., **Van Broeckhoven,C.**, Wilcock,G., Rubinsztajn,D.C.: A presenilin-1 truncating mutation is present in two cases with autopsy-confirmed early-onset Alzheimer's disease. *American Journal of Human Genetics* 62: 70-76 (1998) (I.F.: 10.869)
- Nelis,E., Holmberg,B., Adolfsson,R., Holmgren,G., **Van Broeckhoven,C.**: PMP22 Thr(118)Met: recessive CMT1 mutation or polymorphism? *Nature Genetics* 15: 13-14 (1997) (I.F.: 38.856)
- Hofman,A., Ott,A., Breteler,M.M.B., Bots,M.L., Slooter,A.J.C., van Harskamp,F., van Duijn,C.M., **Van Broeckhoven,C.**, Grobbee,D.E.: Atherosclerosis, apolipoprotein E and the prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *The Lancet* 349: 151-154 (1997) (I.F.: 16.135)
- Oruc,L., Lindblad,K., Verheyen,G.R., Ahlberg,S., Jakovljevic,M., Ivezic,S., Raeymaekers,P., **Van Broeckhoven,C.**, Schalling,M.: CAG repeat expansion in bipolar and unipolar disorders. *American Journal of Human Genetics* 60: 730-732 (1997) (I.F.: 10.244)
- Slooter,A.J.C., Breteler,M.M., Ott,A., **Van Broeckhoven,C.**, van Duijn,C.M.: APOE genotyping in differential diagnosis of Alzheimer's disease. *The Lancet* 348: 334 (1996) (I.F.: 17.948)
- Warner,L.E., Hilz,M.J., Appel,S.H., Killian,J.M., Kolodny,E.H., Karpati,G., Carpenter,S., Watters,G.V., Wheeler,C., Witt,D., Bodell,A., Nelis,E., **Van Broeckhoven,C.**, Lupski,J.R.: Clinical phenotypes of different MPZ (P0) mutations may include Charcot-Marie-Tooth type 1B, Dejerine-Sottas, and congenital hypomyelination. *Neuron* 17(3): 451-460 (1996) (I.F.: 16.953)
- Van Broeckhoven,C.**: Presenilins and Alzheimer disease. *Nature Genetics* 11: 230-232 (1995) (I.F.: 28.543)
- Benomar,A., Krols,L., Stevanin,G., Cancel,G., LeGuern,E., David,G., Ouhabi,H., Martin,J.J., Dürr,A., Zaim,M., Ravisé,N., Busque,C., Penet,C., Van Regemortel,N., Weissenbach,J., Yahyaoui,M., Chkili,T., Agid,Y., **Van Broeckhoven,C.**, Brice,A.: The gene for autosomal dominant cerebellar ataxia with pigmentary macular dystrophy maps to chromosome 3p12-p21.1. *Nature Genetics* 10: 84-88 (1995) (I.F.: 28.543)
- van Duijn,C., **Van Broeckhoven,C.**: Alzheimer's disease and the family effect. *Nature Genetics* 8: 115 (1994) (I.F.: 22.568)
- van Duijn,C.M., de Knijff,P., Cruts,M., Wehnert,A., Havekes,L.M., Hofman,A., **Van Broeckhoven,C.**: Apolipoprotein E4 allele in a population-based study of early-onset Alzheimer's disease. *Nature Genetics* 7: 74-78 (1994) (I.F.: 22.568)
- Kempnaers,B., Verheyen,G.R., Van den Broeck,M., Burke,T., **Van Broeckhoven,C.**, Dhondt,A.A.: Extra-pair paternity results from female preference for high-quality males in the blue tit. *Nature* 357: 494-496 (1992) (I.F.: 25.466)
- Van Broeckhoven,C.**, Backhovens,H., Cruts,M., De Winter,G., Bruylant,M., Cras,P., Martin,J.-J.: Mapping of a gene predisposing to early-onset Alzheimer's disease to chromosome 14q24.3. *Nature Genetics* 2: 335-339 (1992) (I.F.: 22.568)
- Timmerman,V., Nelis,E., Van Hul,W., Nieuwenhuijsen,B.W., Chen,K.L., Wang,S., Ben Othman,K., Cullen,B., Leach,R.J., Hanemann,C.O., De Jonghe,P., Raeymaekers,P., Van Ommen,G.J.B., Martin,J.-J., Müller,H.W., Vance,J.M., Fischbeck,K.H., **Van Broeckhoven,C.**: The peripheral myelin protein gene PMP-22 is contained within the Charcot-Marie-Tooth disease type 1A duplication. *Nature Genetics* 1: 171-175 (1992) (I.F.: 22.568)
- Hendriks,L., van Duijn,C.M., Cras,P., Cruts,M., Van Hul,W., van Harskamp,F., Warren,A., McInnis,M.G., Antonarakis,S.E., Martin,J.-J., Hofman,A., **Van Broeckhoven,C.**: Presenile dementia and cerebral haemorrhage linked to a mutation at codon 692 of the β -amyloid precursor protein gene. *Nature Genetics* 1: 218-221 (1992) (I.F.: 22.568)
- Hoogendijk,J.E., Hensels,G.W., Gabreëls-Festen,A.A.W.M., Gabreëls,F.J.M., Janssen,E.A.M., De Jonghe,P., Martin,J.-J., **Van Broeckhoven,C.**, Valentijn,L.J., Baas,F., De Visser,M., Bolhuis,P.A.: De-novo mutation in hereditary motor and sensory neuropathy type I. *The Lancet* 339: 1081-1082 (1992) (I.F.: 17.332)
- van Duijn,C.M., Hendriks,L., Cruts,M., Hardy,J.A., Hofman,A., **Van Broeckhoven,C.**: Amyloid precursor protein gene mutation in early-onset Alzheimer's disease. *The Lancet* 337: 978 (1991) (I.F.: 17.332)

St. George-Hyslop, P.H., Haines, J.L., Farrer, L.A., Polinsky, R., **Van Broeckhoven, C.**, Goate, A., Crapper McLachlan, D.R., Orr, H., Bruni, A.C., Sorbi, S., Rainero, I., Foncin, J.-F., Pollen, D., Cantu, M., Tupler, R., Voskresenskaya, N., Mayeux, R., Growdon, J., Fried, V.A., Meyers, R.H., Nee, L., Backhovens, H., Martin, J.J., Rossor, M., Owen, M.J., Mullan, M., Percy, M.E., Karlinsky, H., Rich, S., Heston, L., Montesi, M., Mortilla, M., Nacmias, N., Gusella, J.F., Hardy, J.A.: Genetic linkage studies suggest that Alzheimer's disease is not a single homogeneous disorder. *Nature*: 194-197 (1990) (I.F.: 25.466)

Van Broeckhoven, C., Haan, J., Bakker, E., Hardy, J.A., Van Hul, W., Wehnert, A., Vegter-Van der Vlis, M., Roos, R.A.C.: Amyloid β -protein precursor gene and hereditary cerebral hemorrhage with amyloidosis (Dutch). *Science* 248: 1120-1122 (1990) (I.F.: 22.067)

Bakker, E., **Van Broeckhoven, C.**, Bonten, E.J., van de Vooren, M.J., Veenema, H., Van Hul, W., Van Ommen, G.J.B., Vandenberghe, A., Pearson, P.L.: Germline mosaicism and Duchenne muscular dystrophy mutations. *Nature* : 554-556 (1987) (I.F.: 25.466)

Van Broeckhoven, C., Genthe, A.M., Vandenberghe, A., Horsthemke, B., Backhovens, H., Raeymaekers, P., Van Hul, W., Wehnert, A., Gheuens, J., Cras, P., Bruyland, M., Martin, J.-J., Salbaum, M., Multhaup, G., Masters, C.L., Beyreuther, K., Gurling, H.M.D., Mullan, M.J., Holland, A., Barton, A., Irving, N., Williamson, R., Richards, S.-J., Hardy, J.: Failure of familial Alzheimer's disease to segregate with the A4-amyloid gene in several European families. *Nature* : 153-155 (1987) (I.F.: 25.466)